April 14, 1952

My dear Hayes:

Your letter of the 8th has just now arrived. I judge that you will but recently have received mine of the 5th. This crossing of ideas as well as correspondence is coming to be a regular thing.

I think my letter may have anticipated some of the points raised in yours (or vice versa). However, my note, upon a re-reading appears rather obscure, so that I will try to clarify it. I shall not be surprised to find that this messgge will again cross yours, but this kind of exchange of ideas is absolutely indispensable.

First of all, I don't think a detailed comparison of experimental protocol's is essential. There is no doubt we have all run into the same thing, both with respect to the differential fertility of F+ x F- as compared with F+ x F+, and the effct of F-polarity on the segregation ratios. I noticed this about 3 months ago, but was rather puzzled that BM-F- x TL-F+ was much more fertile than BM-F+ x TL-F+ or F- which are about the same. With some further comparisons using other BM and TL stocks, I've come to the conclusion that there is a gradient of F+ potency. Of the stocks you have, the F- would be a zero grade, 58-161 would be +1, and TL-F+ +2. The fertility of a combination would depend on the degree of separation of the parents (along the lines of the Hartmann theory of relative sexuality in the algae). In addition, S^t cells generally can function (almost) exclusively as relative F- . This would account for the very low yields of BM-F+ S^s x TL-F+S^r on streptomycin agar, as compared with the cross x TL-B-S^r (W-1177), There is also an effect of segregation ratio of the S^r factor, but this is not enough to account for the differehce.

As to the segregation ratios, the effect of F-polarity was under our noses almost three years but (as usual?) we missed it until the compatibility story came to light. Filial TL- cultures extracted fromheterozygotes were observed to give ~~kkkx~~ inverted segregations in crosses with 58-161. I thought then that this was evidence for chromosomal aberrations of a simple sort (that the filial stock had acquired the chromosome order of the other parent). Of course, there was no more to it than the F+ character of the filial. All of the results (yours and ours) are compatible with the assumption that the gametic contribution of the F+ parent is defective in some way. We have some stocks which are of higher F+ grade than TLF+, and in these crosses it is again the TL parent's contribution that is favored among the prototrophs.

I hope that you will underatand this counter-Machiavellian gambit (shall we call this "Sciencemanship-- according to Potter"?). But seriousky, I am sure that after we understand each other's terms, we shall find ourselves in much closer agreement that might appear at first.

There is no doubt that there is some unorthodoxy in the sexual mechanism of E. coli, and you are certainly missing no opportunity to expose it. My experience with persistent diploids has given me a certain orientation as to the probabke nature of this peculiarity. You may or may not agree with ~~kk~~ the idea, but I think it more important we don't get into a merely semantic embroil.

We are agreed that the zygote is defective, especially with respect to the genetic contribution of the F+ parent. We can resolve our discussion in these terms: is the defect large or small, compared to the whole genotype; does it originate prior to gamete formation (as I believe you hold), or subsequent to the union of complete gametes? The first question is more readily answered, as the independent evidence from the diploids is quite clearcut.

Faced solely with the prototroph results, and the effect of F-polarity, I probably would have entertained the same hypothesis as you suggest, that recombination is restricted to small blocks of genes. Of all the markers that have been tested, however, only two have proved to be deficient in the diploids: the linked pair- Mal and S. All others have regularly appeared in heterozygous

condition from appropriate crosses. When the Het factor is present, some 10%

of the prototrophs are usually diploid, and in their general behavior they resemble the prototroph sequence, so that I have been confident that the diploids are valid representatives of the zygotes from which the prototrophs normally issue. It requires the consideration, simply, that K-12 has just one chromosome to see how a defect limited to a relatively small region can perturb the apparent segregation behavior of all the other markers: the defective chromosome is simply inviable in the haploid condition. I have fairly direct evidence that F-polarity influences the choice of chromosomes to be eliminated, ile., determines whether the diploids of a given cross will be BM-TL+Lac+V_1^s Mal+S^s/BM+TL-Lac-V_1^r.. .. or BM-TL+Lac+V_1^s.. ../BM+TL-Lac-V_1^rMal-S^r. This is a mysterious phenomenon, but its unorthodoxy is at a somewhat different level from the question of sexuality. In a very few instances, I have obtained diploids that were heterozygous for all of the markers.These in turn have been used in diploid x haploid crosses (via a few obscure tricks) in which the elimination does not seem to occur, so that the derived diploids are, in turn, "complete".

The timing of the defect is somewhat more difficult to be precise about. I had worried about the possibility that the defect was primary (i.e., your hypothesis). The evidence on which I had decided that it probably was not is not compelling, but it still makes sense to me. This has to do with the occurrence of crossing-over in the formation of the diploids. Some of them are, for example, Lac-/Lac- instead of the expected Lac-/Lac+ [there is rather detailed proof that they are diploid homozygous Lac-/Lac- rather than hemizygous Lac-/.. like the Mal-]. These can be accounted for by the occurrence of crossing-over within the zygote prior to establishment of the persistent diploids. A similar sort of thing seems to happen in the defective segment, so that some of the diploids, still hemizygous for this segment are Mal+S^r or Mal-S^s instead of the expected arrangements. A gamete defective for the whole segment could not engender such crossovers. On the other hand, if they derive from "less defective" gametes, why don't these give types hemizygous for S, but not for Mal, or vice versa? Such types simply have not occurred. This is the main reason I have preferred to think of a "segmental elimination", rather than a primary defect, but I may be wrong.

All of this complexity is a bit hard to take, and I have often wondered whether I might not be on the wrong track altogether. But I can interpret the few complete diploids' behavior in no otherway than a straightforward sexual process. That this might go wrong in details is obvious, but it stands as the fundamental pattern. This discussion has reached a point where even a morphological demonstration of the sexual process would hardly alter the issue (unless of course it turns out to be in no way a typical mating reaction). In the present state of our knowledge, descriptive accounts are going to stand up better than premature interpretations. Do we know enough yet of the biology of transformations to be very secure in evolutionary comparisons with sex? I am afraid that much more has been written into my descriptions of K-12 recombination as a sexual process than I had intended, but I knew of no better context to described what one could accomplish by way of a genetic analysis. That is, to my mind, all of our discussion has concerned the description of the sex process that K-12 happens to have. Whether you want to call something a gene-donor or a gamete is immaterial, so long as you have a clear concept and description of its behavior. I've said all this before, in my 1947 paper. If some of the gametes are partially defective, so be it, (but I don't think so).

Sincerely,

Joshua Lederberg